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APPELLANTS' BRIEF Address to: Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Application Number	09/977,358
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	Attorney Docket No.	10030634-2
	Filing Date	Ocober 16, 2001
	First Named Inventor	PIEPER, REMBERT
	Examiner	VENCI, DAVID J.
	Group Art	1641
	Title: IMMUNOSUBTRACTION METHOD FOR SAMPLE PREPARATION FOR 2-DGE	

Sir:

This Brief is filed in support of Appellants' appeal from the Examiner's Rejection dated August 10, 2007. No claims have been allowed. Claims 32, 52, 62-69, 84, 85, 88, 89, 104-107 and 110-113 are pending and appealed herein. A Notice of Appeal was filed on December 7, 2007.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

The Commissioner is hereby authorized to charge deposit account number 50-1078, reference no. 10030634-2 to cover the fee required under 37 C.F.R. §1.17(b) for filing Appellants' brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-1078, reference no. 10030634-2.

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REAL PARTY IN INTEREST

The assignee of record in this application is Large Scale Biology Corporation, 3333 Vaca Valley Parkway, Suite 1000, Vacaville, California, 95688.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

The present application was filed on October 16 with Claims 1-44. During the course of prosecution, Claims 56-113 were added and Claims 1-31, 33-51, 53-61, 70-83, 86, 87, 90-103, 108 and 109 were canceled. Accordingly, Claims 32, 52, 62-69, 84, 85, 88, 89, 104-107 and 110-113 are pending in the present application, all of which stand rejected. All of the rejected claims are appealed herein.

STATUS OF AMENDMENTS

Claims 63, 84, 104 and 111 were filed subsequent to issuance of the Final Rejection. The Advisory Action indicated that these amendments would be entered upon filing of a Notice of Appeal. As a Notice of Appeal has now been filed, these claim amendments have been entered.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is drawn to a method of immunosubtraction for removing abundant proteins from a sample to permit enhancement of detection and resolution of less-abundant proteins in the sample by, for example, two-dimensional gel electrophoresis.

Below is a description of each appealed claim and where support for each can be found in the specification.

Independent claim 63 claims a method for producing and recovering a modified sample, the method including removing at least a first protein and a second

protein from a sample, the removing step including contacting the sample with an affinity binding composition including a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, in which each the solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture in the binding composition; so that when the sample is contacted with the affinity binding composition, the first protein present in the sample binds to the first receptor present on the first solid phase matrix such that the first protein is removed from the sample and the second protein present in the sample binds to the second receptor present on the second solid phase matrix such that the second protein is removed from the sample and the modified sample is thereby produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample (see specification at page 13, lines 4-7; page 15, lines 21-28; page 20, lines 13-26; page 27, lines 9-13; page 28, line 26 through page 29, line 2).

Independent claim 84 claims a method for producing and recovering a modified sample, the method including removing at least a first protein and a second protein from a sample, the removing step including contacting the sample with an affinity binding composition including a plurality of solid phase matrices with a plurality of receptors having different protein binding specificities immobilized thereon such that each solid phase matrix has a different protein binding specificity, in which each the solid phase matrix is a plurality of particles and the plurality of solid phase matrices are present as a mixture in the binding composition, so that when the sample is contacted with the affinity binding composition, the at least two proteins become bound to the affinity binding composition and the proteins are thereby removed from the sample such that the modified sample is produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample (see specification at page 13, lines 4-7; page 15, lines 21-28; page 20, lines 13-26; page 27, lines 9-13; page 28, line 26 through page 29, line 2).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Claims 32, 52, 62-69, 84, 88, 89, 104, 105 and 110-1 13 stand rejected under 35 U.S.C. 102(e) as being anticipated by Hutchens *et al.* (US 6,225,047).

II. Claims 62-64, 66, 84-85, 88-89, 104 and 110-113 stand rejected under 35 U.S.C. 102(b) as being anticipated by Rubenstein (US 5,879,881).

III. Claims 62-64, 66, 84-85, 88-89, 104-107 and 110-113 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ullman *et al.* (US 5,137,808) in view of Rubenstein (US 5,879,881).

ARGUMENT

I. Claims 32, 52, 62-69, 84, 85, 88, 89, 104-107 and 110-113 are not anticipated under 35 U.S.C. § 102(e) by Hutchens *et al.* (US 6,225.047).

With regard to this rejection, the Appellants will argue the rejected claims in Groups as follows:

Group I: Claims 52, 63, 85, 88, 89, 104, 110 and 112 drawn to a method for producing and recovering a modified sample, the method including removing at least a first protein and a second protein from a sample, the removing step including contacting the sample with an affinity binding composition including a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, in which each the solid phase matrix is a plurality of particles

and the first and second solid phase matrices are present as a mixture in the binding composition; so that when the sample is contacted with the affinity binding composition, the first protein present in the sample binds to the first receptor present on the first solid phase matrix such that the first protein is removed from the sample and the second protein present in the sample binds to the second receptor present on the second solid phase matrix such that the second protein is removed from the sample and the modified sample is thereby produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample;

Group II: Claims 64 and 65, drawn to the method of claim 63, in which the affinity binding composition further includes a third receptor immobilized on a third solid phase matrix, capable of specific binding to a third protein but not the first protein or the second protein, in which the third solid phase matrix contacts the first and second solid phase matrices;

Group III: Claims 66 and 67, drawn to the method of claim 63, in which the affinity binding composition further includes a fourth receptor immobilized on a fourth solid phase matrix, capable of specific binding to a fourth protein but not the first protein, the second protein or the third protein, in which the fourth solid phase matrix contacts the first, second, and third solid phase matrices;

Group IV: Claims 68 and 69, drawn to the method of claim 66, in which the affinity binding composition further includes a fifth receptor immobilized on a fifth solid phase matrix, capable of specific binding to a

protein but not the first protein, the second protein, the third protein or the fourth protein, in which the fourth solid phase matrix contacts the first, second, third and fourth solid phase matrices;

Group V: Claims 52, 84, 85, 88, 111 and 113, drawn to a method for producing and recovering a modified sample, the method including removing at least a first protein and a second protein from a sample, the removing step including contacting the sample with an affinity binding composition including a plurality of solid phase matrices with a plurality of receptors having different protein binding specificities immobilized thereon such that each solid phase matrix has a different protein binding specificity, in which each the solid phase matrix is a plurality of particles and the plurality of solid phase matrices are present as a mixture in the binding composition, so that when the sample is contacted with the affinity binding composition, the at least two proteins become bound to the affinity binding composition and the proteins are thereby removed from the sample such that the modified sample is produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample;

Group VI: Claims 105-107, drawn to the method of claim 63, 84, or 85, in which at least two, three or four, respectively, of the proteins are selected from the group consisting of: immunoglobulins, albumin, transferrin, haptoglobin, α_1-antitrypsin, hemopexin, α_1-acid glycoprotein, α2 HS glycoprotein, myosin, transthyretin, α_1-antichymotrypsin, apolipoprotein Al, α_2-macroglobulin, fibrinogen, and prealbumin;

Group VII: Claim 32, drawn to the method of claim 63, 84, 85, 88, or 106 in which at least 50% by weight of all proteins in the sample are removed; and

Group VIII: Claim 62, drawn to the method of claim 63, 84, or 85, in which at least one of the proteins is present at higher abundance than at least one of the plurality of proteins remaining in the sample after removal of the proteins.

Group I: Claims 52, 63, 85, 88, 89, 104, 110 and 112

As described above, independent Claim 63 is drawn to a method for producing and recovering a modified sample, the method including removing at least a first protein and a second protein from a sample, the removing step including contacting the sample with an affinity binding composition including a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, in which each the solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture in the binding composition; so that when the sample is contacted with the affinity binding composition, the first protein present in the sample binds to the first receptor present on the first solid phase matrix such that the first protein is removed from the sample and the second protein present in the sample binds to the second receptor present on the second solid phase matrix such that the second protein is removed from the sample and the modified sample is thereby produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

For the reasons detailed below, the Appellants submit that Hutchens *et al.* (hereinafter "Hutchens," US 6,225,047) fails to anticipate the claimed invention. Specifically, the Appellants submit that Hutchens fails to teach, either expressly or inherently, each element of the claimed method of using an affinity binding composition including a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, in which each solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture in the binding composition. The Appellants argue that none of these elements are taught by Hutchens.

In the Advisory Action of November 2, 2007, the Examiner states that the rejections under U.S.C. § 102 and 103 are maintained for reasons of record because "Applicants' alternative interpretations of the cited prior art do not appear to negate anticipation by portions of the cited prior art that Examiner actually cited in the Final Rejection" (Advisory Action, page 2).

Appellants reply that in reading the "portions of the cited prior art that the Examiner actually cited," one of ordinary skill in the art would rely not only upon the cited portions, but upon the entirety of the reference in order to understand what is communicated by the cited passages. When read in its entirety, Hutchens nowhere communicates to the ordinarily skilled artisan the claimed elements which the Examiner asserts are present in the cited passages. The Examiner here selectively cites portions of Hutchens out of context while ignoring the understanding of the terms used which would be arrived at by an artisan ordinarily skilled in the relevant art in reading the entire reference.

Specifically, in the Final Office Action dated August 10, 2007, the Examiner defined the mixture of a plurality of solid phase matrices with a plurality of receptor types as allegedly found in Hutchens as:

> i. a plurality of receptor types (see *e.g.*, col. 20, line 8, "adsorbent") having different protein binding specificities relative to each other (see *e.g.*, col. 21, line 36, "Incremental or Gradient Adsorbent Surfaces"; see also, col. 13, lines 52-53, "multiplex adsorbent"), each receptor type immobilized on separate particles (see col. 20, lines 9-10, "polymeric or glass bead"), the particles present as a mixture in said affinity binding composition [Office Action, pages 4-5].

The Examiner thereby relies on the cited terms "adsorbent" and "multiplex adsorbent" as used by Hutchens, to assert that Hutchens teaches a plurality of receptor types having different protein binding specificities relative to each other, each receptor type immobilized on separate particles. However, the cited passages of Hutchens do not teach what the Examiner alleges. Hutchens' own explanation of the cited terms is not consistent with the Examiner's assertion. The relevant passage of Hutchens, wherein Hutchens defines both terms, (column 13, lines 47-62) is reproduced below for convenience:

> "Adsorbent" refers to any material capable of adsorbing an analyte. The term "adsorbent" is used herein to refer both to a single material ("monoplex adsorbent") (e.g., a compound or functional group) to which the analyte is exposed, and to a plurality of different materials ("multiplex adsorbent") to which a sample is exposed. The adsorbent materials in a multiplex adsorbent are referred to as "adsorbent species." For example, an addressable location on a substrate can comprise a multiplex adsorbent characterized by many different adsorbent species (e.g., anion exchange materials, metal chelators, or antibodies), having different binding characteristics.
>
> "Adsorb" refers to the detectable binding between an absorbent and an analyte either before or after washing with an eluant (selectivity threshold modifier).

In light of the above passage from Hutchens, one of ordinary skill in the art understands that an addressable location on a substrate bearing an adsorbent as described by Hutchens – whether monoplex or multiplex – binds to "the analyte," or "an analyte," i.e., a single molecule. Hutchens nowhere teaches a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but

not the first protein, where the matrices are present as a mixture, as is claimed.

The Appellants further respectfully point out that the passage in Hutchens, column 36, lines 52-67, which is cited by the Examiner as allegedly describing removal of undesired analytes until a desired analyte remains in the sample, does not teach what the Examiner asserts. Specifically, the cited passage teaches that the particles ("adsorbents") present in different binding conditions are not present as a mixture. The relevant passage of Hutchens at column 36, lines 28-62 is reproduced below for convenience:

A. Methods For Sequentially Extracting Analytes From A Sample

Retentate chromatography involves the analysis of retention of an analyte under a plurality of adsorbent/eluent conditions. One variation of this method is sequential extraction. In sequential extraction a sample is not independently exposed to two different selectivity conditions. Rather, the sample is exposed to a first selectivity condition to extract certain analytes from the sample onto the adsorbent, and leave non-adsorbed analytes in the eluent. Then, the eluent is exposed to a second selectivity condition. This further extracts various analytes from the eluant. Frequently, if the adsorbents in the first and second exposure have different basis for attraction (e.g., normal phase and hydrophobic) the adsorbent will extract a different set of analytes from the eluent. This second eluant is then exposed to a third selectivity condition, and so on. In one method of practicing sequential extraction, the adsorbent is placed at the bottom of a well so that sample can be mixed on top of it. An eluant is added to the adsorbent and after allowing binding between analytes in the sample, the eluant wash is collected. The collected wash is then exposed to a second adsorbent, and analytes are extracted from the sample by binding.

In one embodiment, the goal of sequential extraction is preparative rather than analytical. More specifically, the goal may be to extract all but a desired analyte from the sample. In this case, the sample is usually small, e.g., a few microliters on a spot about a few millimeters in diameter. The adsorbents are selected so as not to adsorb an analyte one wishes not to be depleted from the sample. After several iterations the finally collected wash is depleted of un-desired analytes, leaving the desired ones for subsequent analysis by, for example, desorption spectrometry or traditional chromatographic methods.

In another embodiment, unretained sample is, itself, analyzed for analytes by any analytic technique. Even after a single retention step, this process allows one to examine materials adsorbed to an adsorbent and those analytes that are not adsorbed.

In light of the above passage from Hutchens, one of ordinary skill in the art understands that to perform preparative extraction to remove undesired analytes

leaving a desired analyte remaining in a sample, extractions for each undesired analyte are performed sequentially so that each extraction exposes an analyte to one selectivity condition at a time ("a first selectivity condition," "a second selectivity condition"). Hutchens teaches that each extraction is performed in sequence upon the eluant from each successive extraction/wash step. The alleged matrices are not present as a mixture during an extraction.

As such, this cited passage of Hutchens also fails to teach a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, where the matrices are present as a mixture, as is claimed. It is noted by Appellants that the element of the particles' presence as a mixture is not addressed elsewhere by the instant rejection.

Accordingly:

i. where Hutchens allegedly teaches mixed adsorbents ("multiplex adsorbent"), Hutchens makes clear that all such adsorbents are capable of binding to the same analyte (column 13, lines 47-62); and

ii. where Hutchens allegedly teaches the removal of multiple proteins by using multiple selectivity conditions, Hutchens makes clear that such conditions are used in series, as different extractions each upon the eluant from the preceding extraction (column 36, lines 28-62).

As such, the understanding of the terms in Hutchens which the Examiner uses in order to assert teaching of the instantly claimed elements is not supported by any fair reading of Hutchens itself. Hutchens at least fails to teach a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, in which each solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture, as is claimed.

Accordingly, Hutchens fails to teach each and every limitation of the instant claims.

Group II: Claims 64 and 65

The claims of this group depend directly and indirectly, respectively, from Claim 63 and further include the elements that the affinity binding composition includes a third receptor immobilized on a third solid phase matrix, capable of specific binding to a third protein but not the first protein or the second protein, in which the third solid phase matrix contacts the first and second solid phase matrices. In addition to the above provided arguments, Appellants further submit that Hutchens fails to teach, explicitly or implicitly, a third receptor immobilized on a third solid phase matrix, capable of specific binding to a third protein but not the first or second protein, in which the third solid phase matrix contacts the other solid phase matrices. Put simply, Hutchens does not teach mutual exclusivity of binding capacity, as is required for a set of distinct receptors on matrices to meet the instant claims. As discussed above, and without reiterating the entirety of the argument, where Hutchens allegedly teaches mixed adsorbents ("multiplex adsorbent"), Hutchens makes clear that all such adsorbents are capable of binding to the same analyte (column 13, lines 47-62); and where Hutchens allegedly teaches the removal of multiple proteins by using multiple selectivity conditions, Hutchens makes clear that such conditions are used in series, as different extractions each upon the eluant from the preceding extraction (column 36, lines 28-62), and not as mixtures. As such, one of ordinary skill in the art would neither learn nor find suggestion of the additionally claimed receptor and specificity elements by reading Hutchens.

Group III: Claims 66 and 67

The claims of this group depend directly and indirectly, respectively, from Claim 63 and further include the elements that the affinity binding composition includes a fourth receptor immobilized on a fourth solid phase matrix, capable of specific binding to a fourth protein but not the first protein, the second protein or the third protein, in which the fourth solid phase matrix contacts the first, second, and third solid phase matrices. In addition to the above provided arguments, Appellants further submit that Hutchens fails to teach, explicitly or implicitly, a fourth receptor

immobilized on a fourth solid phase matrix, capable of specific binding to a fourth protein but not the first, second or third protein, in which the fourth solid phase matrix contacts the other solid phase matrices. Put simply, Hutchens does not teach mutual exclusivity of binding capacity, as is required for a set of distinct receptors on matrices to meet the instant claims. As discussed above, and without reiterating the entirety of the argument, where Hutchens allegedly teaches mixed adsorbents ("multiplex adsorbent"), Hutchens makes clear that all such adsorbents are capable of binding to the same analyte (column 13, lines 47-62); and where Hutchens allegedly teaches the removal of multiple proteins by using multiple selectivity conditions, Hutchens makes clear that such conditions are used in series, as different extractions each upon the eluant from the preceding extraction (column 36, lines 28-62), and not as mixtures. As such, one of ordinary skill in the art would neither learn nor find suggestion of the additionally claimed element by reading Hutchens.

Group IV: Claims 68 and 69

The claims of this group depend directly and indirectly, respectively, from Claim 66 and further include the elements that the affinity binding composition further includes a fifth receptor immobilized on a fifth solid phase matrix, capable of specific binding to a protein but not the first protein, the second protein, the third protein or the fourth protein, in which the fourth solid phase matrix contacts the first, second, third and fourth solid phase matrices. In addition to the above provided arguments, Appellants further submit that Hutchens fails to teach, explicitly or implicitly, a fifth receptor immobilized on a fifth solid phase matrix, capable of specific binding to a fifth protein but not the first, second, third or fourth proteins, in which the fifth solid phase matrix contacts the other solid phase matrices. Put simply, Hutchens does not teach mutual exclusivity of binding capacity, as is required for a set of distinct receptors on matrices to meet the instant claims. As discussed above, and without reiterating the entirety of the argument, where Hutchens allegedly teaches mixed adsorbents ("multiplex adsorbent"), Hutchens makes clear that all such adsorbents are capable of binding to the same analyte (column 13, lines 47-62); and where Hutchens allegedly teaches the removal of

multiple proteins by using multiple selectivity conditions, Hutchens makes clear that such conditions are used in series, as different extractions each upon the eluant from the preceding extraction (column 36, lines 28-62), and not as mixtures. As such, one of ordinary skill in the art would neither learn nor find suggestion of the additionally claimed element by reading Hutchens.

Group V: Claims 52, 84, 85, 88, 111 and 113

As described above, independent claim 84 is drawn to a method for producing and recovering a modified sample, the method including removing at least a first protein and a second protein from a sample, the removing step including contacting the sample with an affinity binding composition including a plurality of solid phase matrices with a plurality of receptors having different protein binding specificities immobilized thereon such that each solid phase matrix has a different protein binding specificity, in which each the solid phase matrix is a plurality of particles and the plurality of solid phase matrices are present as a mixture in the binding composition, so that when the sample is contacted with the affinity binding composition, the at least two proteins become bound to the affinity binding composition and the proteins are thereby removed from the sample such that the modified sample is produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Appellants submit that Hutchens *et al.* (hereinafter "Hutchens," US 6,225,047) fails to anticipate the claimed invention. Specifically, the Appellants submit that Hutchens fails to teach, either expressly or inherently, each element of the claimed method using a plurality of solid phase matrices with a plurality of receptors having different protein binding specificities immobilized thereon such that each solid phase matrix has a different protein binding specificity, in which each the solid phase matrix

is a plurality of particles and the plurality of solid phase matrices are present as a mixture in the binding composition. The Appellants argue that none of these elements are taught by Hutchens.

In the Advisory Action of November 2, 2007, the Examiner states that the rejections under U.S.C. § 102 and 103 are maintained for reasons of record because "Applicants' alternative interpretations of the cited prior art do not appear to negate anticipation by portions of the cited prior art that Examiner actually cited in the Final Rejection" (Advisory Action, page 2).

Appellants reply that, as noted above, in reading the "portions of the cited prior art that the Examiner actually cited," one of ordinary skill in the art would depend not only upon the cited portions but upon the entirety of the reference in order to understand what is communicated by the cited passages. When read in its entirety, Hutchens nowhere communicates to the ordinarily skilled artisan the claimed elements which the Examiner asserts are present in the cited passages. The Examiner here selectively cites portions of Hutchens while ignoring the understanding of the terms used which would be arrived at by an artisan ordinarily skilled in the relevant art.

Appellants submit that the arguments made above for Group I apply to the claims of the present group. Briefly, and without reiterating the entirety of the argument, where Hutchens allegedly teaches mixed adsorbents ("multiplex adsorbent"), Hutchens makes clear that all such adsorbents are capable of binding to the same analyte (column 13, lines 47-62); and where Hutchens allegedly teaches the removal of multiple proteins by using multiple selectivity conditions, Hutchens makes clear that such conditions are used in series, as different extractions each upon the eluant from the preceding extraction (column 36, lines 28-62), and not as mixtures. As such, one of ordinary skill in the art would neither learn nor find suggestion of the additionally claimed plurality of receptor and specificities element by reading Hutchens. Put simply, Hutchens does not teach mutual exclusivity of binding capacity, as is required for a set of distinct receptors on matrices to meet the

instant claims. As such, the understanding of the terms in Hutchens which the Examiner uses in order to assert teaching of the instantly claimed elements is not supported by any fair reading of Hutchens itself. Hutchens at least fails to teach a plurality of receptors having different protein binding specificities immobilized thereon such that each solid phase matrix has a different protein binding specificity, in which each solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture, as is claimed. Accordingly, Hutchens fails to teach each and every limitation of the instant claims.

Group VI: Claims 105-107

Claims 105-107 depend from any of Claims 63, 84, or 85, and further include the element in which at least two, three or four, respectively, of the proteins are selected from the group consisting of: immunoglobulins, albumin, transferrin, haptoglobin, α_1-antitrypsin, hemopexin, α_1-acid glycoprotein, α2 HS glycoprotein, myosin, transthyretin, α_1-antichymotrypsin, apolipoprotein Al, α_2-macroglobulin, fibrinogen, and prealbumin. In addition to the above provided arguments, Appellants further submit that Hutchens fails to teach the removal from the sample of any two of the claimed proteins. Accordingly, Hutchens additionally fails to teach the limitations of this claim group.

Group VII: Claim 32

Claim 32 depends from any of Claims 63, 84, 85, 88, or 106 and further includes the element in which at least 50% by weight of all proteins in the sample are removed. In addition to the above provided arguments, Appellants further submit that Hutchens fails to teach the removal of any percentage or proportion of total protein from the sample by the method of Hutchens. Accordingly, Hutchens additionally fails to teach the limitations of this claim group.

Group VIII: Claim 62

Claim 62 depends from any of Claims 63, 84 or 85 and further includes the element in which at least one of the proteins is present at higher abundance than at least one of the plurality of proteins remaining in the sample after removal of the

proteins. In addition to the above provided arguments, Appellants further submit that Hutchens nowhere discusses the greater abundance of a protein to be removed relative to any other protein in the sample of Hutchens. Accordingly, Hutchens additionally fails to teach the limitations of this claim group.

In view of the discussion above, the Appellants submit that Hutchens *et al.* fail to anticipate the claims of Groups I through VIII and respectfully request reversal of this rejection.

II. Claims 62-64, 66, 84-85, 88-89, 104 and 110-113 are not anticipated under 35 U.S.C. § 102(b) by Rubenstein (US 5,879,881).

With regard to this rejection, the Appellants will argue the rejected claims in Groups as follows:

Group I: Claims 63, 85, 88, 104, 110 and 112 drawn to a method for producing and recovering a modified sample, the method including removing at least a first protein and a second protein from a sample, the removing step including contacting the sample with an affinity binding composition including a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, in which each the solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture in the binding composition; so that when the sample is contacted with the affinity binding composition, the first protein present in the sample binds to the first receptor present on the

first solid phase matrix such that the first protein is removed from the sample and the second protein present in the sample binds to the second receptor present on the second solid phase matrix such that the second protein is removed from the sample and the modified sample is thereby produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample;

Group II: Claims 64 and 65, drawn to the method of claim 63, in which the affinity binding composition further includes a third receptor immobilized on a third solid phase matrix, capable of specific binding to a third protein but not the first protein or the second protein, in which the third solid phase matrix contacts the first and second solid phase matrices;

Group III: Claims 66 and 67, drawn to the method of claim 63, in which the affinity binding composition further includes a fourth receptor immobilized on a fourth solid phase matrix, capable of specific binding to a fourth protein but not the first protein, the second protein or the third protein, in which the fourth solid phase matrix contacts the first, second, and third solid phase matrices;

Group IV: Claims 68 and 69, drawn to the method of claim 66, in which the affinity binding composition further includes a fifth receptor immobilized on a fifth solid phase matrix, capable of specific binding to a protein but not the first protein, the second protein, the third protein or the fourth protein, in which the fourth solid phase matrix contacts the first, second, third and fourth solid phase matrices;

Group V: Claims 52, 84, 85, 88, 111 and 113, drawn to a method for producing and recovering a modified sample, the method including removing at least a first protein and a second protein from a sample, the removing step including contacting the sample with an affinity binding composition including a plurality of solid phase matrices with a plurality of receptors having different protein binding specificities immobilized thereon such that each solid phase matrix has a different protein binding specificity, in which each the solid phase matrix is a plurality of particles and the plurality of solid phase matrices are present as a mixture in the binding composition, so that when the sample is contacted with the affinity binding composition, the at least two proteins become bound to the affinity binding composition and the proteins are thereby removed from the sample such that the modified sample is produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample;

Group VI: Claim 89, drawn to the method of claim 63, 84, or 85, in which the receptors are recombinantly produced;

Group VII: Claims 105-107, drawn to the method of claim 63, 84, or 85, in which at least two, three or four, respectively, of the proteins are selected from the group consisting of: immunoglobulins, albumin, transferrin, haptoglobin, α_1-antitrypsin, hemopexin, α_1-acid glycoprotein, α2 HS glycoprotein, myosin, transthyretin, α_1-antichymotrypsin, apolipoprotein Al, α_2-macroglobulin, fibrinogen, and prealbumin;

Group VIII: Claim 32, drawn to the method of claim 63, 84, 85, 88, or 106 in which at least 50% by weight of all proteins in the sample are removed;

Group IX: Claim 52, drawn to the method of claim 63, 84, or 85, further including the step of analyzing a plurality of proteins remaining in the modified sample; and

Group X: Claim 62, drawn to the method of claim 63, 84, or 85, in which at least one of the proteins is present at higher abundance than at least one of the plurality of proteins remaining in the sample after removal of the proteins.

Group I: Claims 63, 85, 88, 104, 110 and 112

As described above, independent Claim 63 is drawn to a method for producing and recovering a modified sample, the method including removing at least a first protein and a second protein from a sample, the removing step including contacting the sample with an affinity binding composition including a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, in which each the solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture in the binding composition; so that when the sample is contacted with the affinity binding composition, the first protein present in the sample binds to the first receptor present on the first solid phase matrix such that the first protein is removed from the sample and the second protein present in the sample binds to the second receptor present on the second solid phase matrix such that the second protein is removed from the sample and the modified sample is thereby produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.

Verdegaal Bros. v. Union Oil of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

For the reasons detailed below, the Appellants submit that Rubenstein (US 5,879,881) fails to anticipate the claimed invention. Specifically, the Appellants submit that Rubenstein fails to teach, either expressly or inherently, each element of the claimed method using an affinity binding composition including a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, in which each solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture in the binding composition. The Appellants argue that none of these elements are taught by Rubenstein.

In the Advisory Action of November 2, 2007, the Examiner states that the rejections under U.S.C. § 102 and 103 are maintained for reasons of record because "Applicants' alternative interpretations of the cited prior art do not appear to negate anticipation by portions of the cited prior art that Examiner actually cited in the Final Rejection" (Advisory Action, page 2).

Appellants reply that in reading the "portions of the cited prior art that the Examiner actually cited," one of ordinary skill in the art would rely not only upon the cited portions, but upon the entirety of the reference in order to understand what is communicated by the cited passages. When read in its entirety, Rubenstein nowhere communicates to the ordinarily skilled artisan the claimed elements which the Examiner asserts are present in the cited passages. The Examiner here selectively cites portions of Rubenstein out of context while ignoring the understanding of the terms used which would be arrived at by an artisan ordinarily skilled in the relevant art in reading the entire reference.

Specifically, in the Final Office Action dated August 10, 2007, the Examiner

defines the plurality of particles present as a mixture as allegedly found in Rubenstein as:

> i. a plurality of receptor types having different protein binding specificities relative to each other (see, e.g., col. 6, line 5, "different enzyme labeled antibodies"; see also, line 20, "panel of allergens"; see also, lines 35-36, "different receptor"), each receptor type immobilized on separate particles (see *e.g.*, col. 6, line 7, "groups of microspheres"; see also, lines 15-16, "distinct groups of microspheres"; see also, line 34, "groups of microspheres"), the particles present as a mixture in said affinity binding composition

The Examiner defines the removing proteins from a sample as allegedly found in Rubenstein as:

> removing (see e.g., col. 6, line 20, "capturing"; see also, line 35, "the capture") at least a first protein and a second protein (see e.g., col. 6, line 1, "at least two selected analytes"; see also, lines 20-21, "IgE antibodies"; see also, lines'35-36, "different ligands") from a sample, said removing step comprising: contacting the sample with an affinity binding composition (see e.g., col. 6, line 8, "porous matrix"; see also, line 19, "matrix"; see also, Fig. 4, matrix 10) [Office Action, page 5].

The Examiner defines the step of recovering as allegedly found in Rubenstein as:

> (2) recovering the modified sample (see Fig. 6, "second absorbent member 38") (Office Action, page 6).

The Examiner thereby relies on the cited terms to assert that Rubenstein teaches a plurality of receptor types having different protein binding specificities relative to each other, each receptor type immobilized on separate particles. However, the cited passages of Rubenstein do not teach what the Examiner alleges. Rubenstein's own explanation of the cited terms is not consistent with the Examiner's assertion. The relevant passage of Rubenstein at column 5, lines 44-65, is reproduced below for convenience:

A preferred solid phase system of the present invention comprises plural groups of microspheres entrapped in discrete zones, preferably in a predetermined pattern, within the matrix. Each group of microspheres is bound, prior to entrapment, with a different receptor, such as an antibody or antigen capable of capturing a different ligand of interest. Accordingly, in one embodiment of the invention, each group of microspheres comprises a population of microspheres bound with the same antibody, antigen or other receptor selected for use in the assay. Alternatively, a group of microspheres may comprise a mixture of microspheres to which are bound different receptors. For example, in the case of an immunoassay for an antigen, each group of microspheres may comprise at least two subpopulations of microspheres wherein each subpopulation is bound with an antibody, preferably a monoclonal antibody, capable of binding with a different determinant or epitops of the antigen. Preferably, the monoclonal antibodies bound with the subpopulations of microspheres comprising a distinct group of microspheres are selected to have a specific reactivity with non-interfering epitopes of the target ligand, thereby enhancing the sensitivity and specificity of the assay.

In light of the above passage from Rubenstein, one of ordinary skill in the art understands that each group of microspheres in a discrete zone, whether bearing a single receptor or multiple receptors, binds to "the target ligand," e.g., "the antigen," i.e., a single molecule. As such, Rubenstein at best fails to teach that the first and second solid phase matrices are present as a mixture in the binding composition, as is claimed. Instead, Rubenstein teaches in the above passage and throughout the reference that microspheres with binding specificities for different proteins are present in different zones, and not as a mixture.

The Appellants further respectfully point out that, throughout the disclosure of Rubenstein, the alleged proteins being removed from a sample ("at least two selected analytes"; see also, lines 20-21, "IgE antibodies"; see also, lines'35-36, "different ligands") are recovered by attachment to the sold phase matrix(see e.g., col. 6, line 20, "capturing"; see also, line 35, "the capture") at least a first protein and a second protein (see e.g., col. 6, line 1, "at least two selected analytes"; see also, lines 20-21, "IgE antibodies"; see also, lines'35-36, "different ligands").

As such, the cited proteins are not absorbed by the cited second absorbent member (see Fig. 6, "second absorbent member 38"), consistent with the fact that Rubenstein is directed to a positive, not negative, selection method. Specifically, the

"sample" which Rubenstein instructs be recovered throughout the disclosure is what is conjugated to the beads.

As such, Rubenstein nowhere teaches that the contents of the cited second absorbent member (see Fig. 6, "second absorbent member 38") are recovered. Instead, upon reading Rubenstein, one of ordinary skill in the art understands that the cited second absorbent member is present, first, to draw fluid through the filter containing the beads which trap the sample (please see, by way of example, Column 7, lines 15-37, wherein the function of the second member is explained), and second, as a waste trap (please see column 8, lines 18-59, describing the use of the device, in which several fluids are added to the apparatus in series, including analyte containing, receptor conjugate, enzymatic detection fluid and wash fluids, all of which are drawn into the cited second absorbent member; see also Examples I and II at columns 9 and 10, both substantiating this understanding of the function of the cited second absorbent member). It is nowhere taught by Rubenstein that the contents of the cited second absorbent member are recovered.

Accordingly, Rubenstein additionally fails to teach a method such that when the sample is contacted with the affinity binding composition the proteins are removed from the sample and the modified sample is thereby produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample, as is claimed.

Group II: Claims 64 and 65

The claims of this group depend directly and indirectly, respectively, from Claim 63 and further include the elements that the affinity binding composition includes a third receptor immobilized on a third solid phase matrix, capable of specific binding to a third protein but not the first protein or the second protein, in which the third solid phase matrix contacts the first and second solid phase matrices. In addition to the above provided arguments, Appellants further submit that Rubenstein fails to teach, explicitly or implicitly, a third receptor immobilized on a third solid phase matrix, capable of specific binding to a third protein but not the first

or second protein, in which the third solid phase matrix contacts the other solid phase matrices. As discussed above, and without reiterating the entirety of the argument, where Rubenstein allegedly teaches mixed adsorbents, Rubenstein makes clear that that each group of microspheres in a discrete zone, whether bearing a single receptor or multiple receptors, binds to "the target ligand," e.g., "the antigen," i.e., a single molecule, and that microspheres with binding specificities for different proteins are present in different discrete zones, and not as a mixture. Where Rubenstein allegedly teaches the removal of multiple proteins from a sample, Rubenstein makes clear that the alleged proteins are not absorbed by the cited second absorbent member, consistent with the fact that Rubenstein is directed to a positive, not negative, selection method. Specifically, the "sample" which Rubenstein instructs be recovered throughout the disclosure is what is conjugated to the beads, not what is absorbed by the cited absorbent member. As such, one of ordinary skill in the art would neither learn nor find suggestion of the additionally claimed matrix and specificity elements present in contact with the other matrices by reading Rubenstein.

Group III: Claims 66 and 67

The claims of this group depend directly and indirectly, respectively, from Claim 63 and further include the elements that the affinity binding composition includes a fourth receptor immobilized on a fourth solid phase matrix, capable of specific binding to a fourth protein but not the first protein, the second protein or the third protein, in which the fourth solid phase matrix contacts the first, second, and third solid phase matrices. In addition to the above provided arguments, Appellants further submit that Rubenstein fails to teach, explicitly or implicitly, a fourth receptor immobilized on a fourth solid phase matrix, capable of specific binding to a fourth protein but not the first, second or third protein, in which the fourth solid phase matrix contacts the other solid phase matrices. As discussed above, and without reiterating the entirety of the argument, where Rubenstein allegedly teaches mixed adsorbents, Rubenstein makes clear that that each group of microspheres in a discrete zone, whether bearing a single receptor or multiple receptors, binds to "the target ligand," e.g., "the antigen," i.e., a single molecule, and that microspheres with

binding specificities for different proteins are present in different discrete zones, and not as a mixture. Where Rubenstein allegedly teaches the removal of multiple proteins from a sample, Rubenstein makes clear that the alleged proteins are not absorbed by the cited second absorbent member, consistent with the fact that Rubenstein is directed to a positive, not negative, selection method. Specifically, the "sample" which Rubenstein instructs be recovered throughout the disclosure is what is conjugated to the beads, not what is absorbed by the cited absorbent member. As such, one of ordinary skill in the art would neither learn nor find suggestion of the additionally claimed matrix and specificity elements present in contact with the other matrices by reading Rubenstein.

Group IV: Claims 68 and 69

The claims of this group depend directly and indirectly, respectively, from Claim 66 and further include the elements that the affinity binding composition further includes a fifth receptor immobilized on a fifth solid phase matrix, capable of specific binding to a protein but not the first protein, the second protein, the third protein or the fourth protein, in which the fourth solid phase matrix contacts the first, second, third and fourth solid phase matrices. In addition to the above provided arguments, Appellants further submit that Rubenstein fails to teach, explicitly or implicitly, a fifth receptor immobilized on a fifth solid phase matrix, capable of specific binding to a fifth protein but not the first, second, third or fourth proteins, in which the fifth solid phase matrix contacts the other solid phase matrices. As discussed above, and without reiterating the entirety of the argument, where Rubenstein allegedly teaches mixed adsorbents, Rubenstein makes clear that that each group of microspheres in a discrete zone, whether bearing a single receptor or multiple receptors, binds to "the target ligand," e.g., "the antigen," i.e., a single molecule, and that microspheres with binding specificities for different proteins are present in different discrete zones, and not as a mixture. Where Rubenstein allegedly teaches the removal of multiple proteins from a sample, Rubenstein makes clear that the alleged proteins are not absorbed by the cited second absorbent member, consistent with the fact that Rubenstein is directed to a positive, not negative, selection method. Specifically, the "sample" which Rubenstein instructs

be recovered throughout the disclosure is what is conjugated to the beads, not what is absorbed by the cited absorbent member. As such, one of ordinary skill in the art would neither learn nor find suggestion of the additionally claimed matrix and specificity elements present in contact with the other matrices by reading Rubenstein.

Group V: Claims 52, 84, 85, 88, 111 and 113

As described above, independent claim 84 is drawn to a method for producing and recovering a modified sample, the method including removing at least a first protein and a second protein from a sample, the removing step including contacting the sample with an affinity binding composition including a plurality of solid phase matrices with a plurality of receptors having different protein binding specificities immobilized thereon such that each solid phase matrix has a different protein binding specificity, in which each the solid phase matrix is a plurality of particles and the plurality of solid phase matrices are present as a mixture in the binding composition, so that when the sample is contacted with the affinity binding composition, the at least two proteins become bound to the affinity binding composition and the proteins are thereby removed from the sample such that the modified sample is produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

For the reasons detailed below, the Appellants submit that Rubenstein (US 5,879,881) fails to anticipate the claimed invention. Specifically, the Appellants submit that Rubenstein fails to teach, either expressly or inherently, each element of the claimed method using a plurality of solid phase matrices with a plurality of receptors having different protein binding specificities immobilized thereon such that each solid phase matrix has a different protein binding specificity, in which each the

solid phase matrix is a plurality of particles and the plurality of solid phase matrices are present as a mixture in the binding composition, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample. The Appellants argue that none of these elements are taught by Rubenstein.

In the Advisory Action of November 2, 2007, the Examiner states that the rejections under U.S.C. § 102 and 103 are maintained for reasons of record because "Applicants' alternative interpretations of the cited prior art do not appear to negate anticipation by portions of the cited prior art that Examiner actually cited in the Final Rejection" (Advisory Action, page 2).

Appellants reply that in reading the "portions of the cited prior art that the Examiner actually cited," one of ordinary skill in the art would rely not only upon the cited portions, but upon the entirety of the reference in order to understand what is communicated by the cited passages. When read in its entirety, Rubenstein nowhere communicates to the ordinarily skilled artisan the claimed elements which the Examiner asserts are present in the cited passages. The Examiner here selectively cites portions of Rubenstein out of context while ignoring the understanding of the terms used which would be arrived at by an artisan ordinarily skilled in the relevant art in reading the entire reference.

Appellants submit that the arguments made above for Group I apply to the claims of the present group. Briefly, and without reiterating the entirety of the argument, where Rubenstein allegedly teaches mixed adsorbents, Rubenstein makes clear that that each group of microspheres in a discrete zone, whether bearing a single receptor or multiple receptors, binds to "the target ligand," e.g., "the antigen," i.e., a single molecule, and that microspheres with binding specificities for different proteins are present in different discrete zones, and not as a mixture. Where Rubenstein allegedly teaches the removal of multiple proteins from a sample, Rubenstein makes clear that the alleged proteins are not absorbed by the cited second absorbent member, consistent with the fact that Rubenstein is directed to a positive, not negative, selection method. Specifically, the "sample" which Rubenstein

instructs be recovered throughout the disclosure is what is conjugated to the beads, not what is absorbed by the cited absorbent member. As such, one of ordinary skill in the art would neither learn nor find suggestion of by reading Rubenstein the claimed plurality of matrices present as a mixture, nor the method of producing a modified sample in which the modified sample is not bound by a solid phase matrix; nor recovery of that modified sample.

Group VI: Claim 89

Claim 32 depends from any of Claims 63, 84 or 85 and further includes the element in which the receptors are recombinantly produced. In addition to the above provided arguments, Appellants further submit that, although Rubenstein discusses the use of monoclonal antibodies, Rubenstein nowhere teaches, explicitly or implicitly, the use of recombinantly produced receptors. Accordingly, Rubenstein additionally fails to teach the limitations of this claim group.

Group VII: Claims 105-107

Claims 105-107 depend from any of Claims 63, 84, or 85, and further include the element in which at least two, three or four, respectively, of the proteins are selected from the group consisting of: immunoglobulins, albumin, transferrin, haptoglobin, α_1-antitrypsin, hemopexin, α_1-acid glycoprotein, α2 HS glycoprotein, myosin, transthyretin, α_1-antichymotrypsin, apolipoprotein Al, α_2-macroglobulin, fibrinogen, and prealbumin. In addition to the above provided arguments, Appellants further submit that Rubenstein fails to teach the removal from the sample of any two of the claimed proteins. Accordingly, Rubenstein additionally fails to teach the limitations of this claim group.

Group VIII: Claim 32

Claim 32 depends from any of Claims 63, 84, 85, 88, or 106 and further includes the element in which at least 50% by weight of all proteins in the sample are removed. In addition to the above provided arguments, Appellants further submit that Rubenstein fails to teach the removal of any percentage or proportion of total

protein from the sample by the method of Rubenstein. Accordingly, Rubenstein additionally fails to teach the limitations of this claim group.

Group IX: Claim 52

Claim 52 depends from any of Claims 63, 84 or 85 and further includes the step of analyzing a plurality of proteins remaining in the modified sample. In addition to the above provided arguments, Appellants further submit that Rubenstein nowhere teaches the analysis of proteins remaining in the modified sample. Accordingly, Rubenstein additionally fails to teach the limitations of this claim group.

Group X: Claim 62

Claim 62 depends from any of Claims 63, 84 or 85 and further includes the element in which at least one of the proteins is present at higher abundance than at least one of the plurality of proteins remaining in the sample after removal of the proteins. In addition to the above provided arguments, Appellants further submit that Rubenstein nowhere discusses the greater abundance of a protein to be removed relative to any other protein in the sample of Rubenstein. Accordingly, Rubenstein additionally fails to teach the limitations of this claim group.

In view of the discussion above, the Appellants submit that Rubenstein fails to anticipate the claims of Groups I through X and respectfully request reversal of this rejection.

III. Claims 62-64, 66, 84-85, 88-89, 104-107 and 110-113 are not obvious under 35 U.S.C. § 103(a) over Ullman et al. (US 5,137,808) in view of Rubenstein (US 5,879,881).

With regard to this rejection, the Appellants will argue the rejected claims in Groups as follows:

Group I: Claims 63, 85, 88, 104-107, 110 and 112 drawn to a method for producing and recovering a modified sample, the method including removing at least a

first protein and a second protein from a sample, the removing step including contacting the sample with an affinity binding composition including a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, in which each the solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture in the binding composition; so that when the sample is contacted with the affinity binding composition, the first protein present in the sample binds to the first receptor present on the first solid phase matrix such that the first protein is removed from the sample and the second protein present in the sample binds to the second receptor present on the second solid phase matrix such that the second protein is removed from the sample and the modified sample is thereby produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample;

Group II: Claims 64 and 65, drawn to the method of claim 63, in which the affinity binding composition further includes a third receptor immobilized on a third solid phase matrix, capable of specific binding to a third protein but not the first protein or the second protein, in which the third solid phase matrix contacts the first and second solid phase matrices;

Group III: Claims 66 and 67, drawn to the method of claim 63, in which the affinity binding composition further

includes a fourth receptor immobilized on a fourth solid phase matrix, capable of specific binding to a fourth protein but not the first protein, the second protein or the third protein, in which the fourth solid phase matrix contacts the first, second, and third solid phase matrices;

Group IV: Claims 68 and 69, drawn to the method of claim 66, in which the affinity binding composition further includes a fifth receptor immobilized on a fifth solid phase matrix, capable of specific binding to a protein but not the first protein, the second protein, the third protein or the fourth protein, in which the fourth solid phase matrix contacts the first, second, third and fourth solid phase matrices;

Group V: Claims 52, 84, 85, 88, 111 and 113, drawn to a method for producing and recovering a modified sample, the method including removing at least a first protein and a second protein from a sample, the removing step including contacting the sample with an affinity binding composition including a plurality of solid phase matrices with a plurality of receptors having different protein binding specificities immobilized thereon such that each solid phase matrix has a different protein binding specificity, in which each the solid phase matrix is a plurality of particles and the plurality of solid phase matrices are present as a mixture in the binding composition, so that when the sample is contacted with the affinity binding composition, the at least two proteins become bound to the affinity binding composition and the proteins are thereby removed from the sample such that the modified sample is produced,

in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample;

Group VI: Claim 89, drawn to the method of claim 63, 84, or 85, in which the receptors are recombinantly produced;

Group VII: Claim 32, drawn to the method of claim 63, 84, 85, 88, or 106 in which at least 50% by weight of all proteins in the sample are removed;

Group VIII: Claim 52, drawn to the method of claim 63, 84, or 85, further including the step of analyzing a plurality of proteins remaining in the modified sample; and

Group IX: Claim 62, drawn to the method of claim 63, 84, or 85, in which at least one of the proteins is present at higher abundance than at least one of the plurality of proteins remaining in the sample after removal of the proteins.

Group I: Claims 63, 85, 88, 104-107, 110 and 112

The Appellants argue below that the Examiner's *prima facie* case of obviousness is deficient because the combined teachings of the cited prior art fail to render the claimed invention obvious.

In *Graham v. John Deere*, the Supreme Court set out a framework for applying the statutory language of 35 U.S.C. § 103. *Graham v. John Deere*, 383 US 1; 148 USPQ 459 (1966). This framework was reiterated in the Court's recent *KSR v. Teleflex Inc.* opinion, as follows:

> "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary

considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented."

KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1734 (2007).

The above framework may be restated as the following four factual inquires:

(A) Determining the scope and contents of the prior art;

(B) Ascertaining the differences between the prior art and the claims in issue;

(C) Resolving the level of ordinary skill in the pertinent art; and

(D) Evaluating evidence of secondary considerations.

With respect to framework elements A and B, courts have held that the reference or references cited in a rejection based on obviousness must teach or suggest all the elements of the claimed invention. "Subsumed within the Graham factors is a subsidiary requirement articulated by this court that where, as here, all claim limitations are found in a number of prior art references, the burden falls on the challenger of the patent to show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Pfizer v. Apotex*, 82 U.S.P.Q.2d 1321, 1330 (Fed. Cir. 2007). *See also Pharmastem Therapeutics v. Viacell et al.*, 83. U.S.P.Q. 2d 1289, 1302 (Fed. Cir. 2007) ("the burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make [every element of] the composition or device, or carry out the [entire] claimed process, and would have had a reasonable expectation of success in doing so," (*citing KSR Int'l Co. v. Teleflex Inc.*, 82. U.S.P.Q.2d 1385 (2007); and see *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 2007 U.S. App. LEXIS 14308 (Fed. Cir. 2007) ("[t]he Supreme Court recently explained that 'a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently,

known in the prior art,' (*citing KSR Int'l Co.* at 1741); and see *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 80 U.S.P.Q.2d 1641, 1646 (Fed. Cir. 2006) ("[once] all claim limitations are found in a number of prior art references, the factfinder must determine '[w]hat the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references,' (*citing In re Fulton*, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004))).

The requirement that the combination of references teach or suggest all elements of the claimed invention has been endorsed by the Patent & Trademark Office. According to the post-KSR Patent Office promulgated examination guidelines on determination of obviousness, when office personnel reject claims by attempting to combine prior art elements according to allegedly known methods to yield predictable results, the Office must resolve the *Graham* factual inquiries and articulate:

> (1) "a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;"
>
> (2) "a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately; and"
>
> (3) "a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable." (Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007 / Notices at 57529, *citing KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1395 (US 2007)).

Thus, the rationale to support a conclusion that a claim would have been obvious is that "all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions." *Id.* at 57529.

The Appellants submit that the combined teachings of Ullman *et al.* (hereinafter "Ullman," US 5,137,808) in view of Rubenstein (US 5,879,881) fail to teach or suggest each and every element of the claimed invention.

As noted above, the claims of this Group are drawn to a method for producing and recovering a modified sample, the method including removing at least a first protein and a second protein from a sample, the removing step including contacting the sample with an affinity binding composition including a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, in which each solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture in the binding composition; so that when the sample is contacted with the affinity binding composition, the first protein present in the sample binds to the first receptor present on the first solid phase matrix such that the first protein is removed from the sample and the second protein present in the sample binds to the second receptor present on the second solid phase matrix such that the second protein is removed from the sample and the modified sample is thereby produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample.

In making this rejection, the Examiner has alleged that Ullman teaches all the elements of the claims with the exception of a plurality of receptor types having different protein binding specificities relative to each other, each receptor type immobilized on separate particles, the particles present as a mixture in the affinity binding composition, for which elements the Examiner turns to Rubenstein. The Appellants submit that the references, individually and in combination, fail to teach or suggest what is alleged by the Examiner.

In the Advisory Action of November 2, 2007, the Examiner states that the rejections under U.S.C. § 102 and 103 are maintained for reasons of record because "Applicants' alternative interpretations of the cited prior art do not appear to

negate anticipation by portions of the cited prior art that Examiner actually cited in the Final Rejection" (Advisory Action, page 2).

Appellants reply that in reading the "portions of the cited prior art that the Examiner actually cited," one of ordinary skill in the art would rely not only upon the cited portions, but upon the entirety of the reference in order to understand what is communicated by the cited passages. When read in their entirety, the references do not communicate to the ordinarily skilled artisan the claimed elements that the Examiner asserts are present in the cited passages. The Examiner here selectively cites portions of Ullman and Rubenstein out of context while ignoring the understanding of the terms used which would be arrived at by an artisan ordinarily skilled in the relevant art in reading the entire references.

First, the Appellants point out that the cited failure by Ullman to teach a plurality of receptor types present as a mixture does not exhaust the deficiencies of Ullman. Specifically, Ullman additionally fails to teach the step of recovering the sample, both modified and unmodified.

The Examiner defines the method for producing a modified sample as allegedly found in Ullman as:

> (1) removing (see Abstract, "capturing") at least a first protein and a second protein (see col. 20, lines 32-44) from a sample, said removing step comprising: contacting the sample with an affinity binding composition (see Fig. 1A, "immunosorbing zone 84");
>
> (2) recovering the modified sample (see Fig. 1A, "absorbent means 20"; see col. 16, lines 29-32).

The Appellants submit that the cited passages do not teach what the Examiner alleges. The Appellants respectfully point out that, throughout the disclosure of Ullman, the proteins being detected (see col. 20, lines 32-44) are non-diffusively immobilized by attachment to the an affinity binding composition (see Fig. 1A, "immunosorbing zone 84") . They are absorbed by the cited absorbent means (see Fig. 1A, "absorbent means 20"; see col. 16, lines 29-32), consistent with the

fact that Ullman is directed to detecting the contents of the apparatus within the strip of bibulous material, but not removing any content from it (note especially that all absorptive materials described are “non-removably confined,” in the housing, throughout the reference). Specifically, in all descriptions of the use of the invention by Ullman, no introduced sample is at any point recovered or made recoverable from the apparatus. This is consistent with the fact that Ullman is directed to a diagnostic, not preparative, device which is not designed to provide a means to recover samples. If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti* 123 USPQ 349 (CCPA 1959). If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon* 221 USPQ 1125 (Fed. Cir. 1984).

As such, Ullman nowhere teaches that the contents of the cited absorbent means (see Fig. 1A, "absorbent means 20"; see col. 16, lines 29-32) are recovered. Instead, upon reading Ullman, one of ordinary skill in the art understands that the cited absorbent means is present, first, to draw fluid through the immunosorbing zone which retains the sample and second, incidentally, as a **waste trap** (please see, by way of example, column 10, lines 36-53, wherein the function of the absorbent means is explained, specifically, as a pump to pump liquid through and out of the immunosorbing zone; column 12, lines 47-54, wherein liquid absorbing member 20 is confined in a recessed area; Figures 1-6, wherein the absorbing member is in all cases placed in such a way as to be inaccessible).

Further, exemplary applications of the apparatus of Ullman (please see column 18, line 28 through column 21) all support this understanding of the diagnostic function of the apparatus and the use of cited absorbent means 20 as a waste trap. Fluids including analyte-containing, label-containing, and wash fluids are all drawn through strip 18 into the absorbent means 20 (see Figure 1A). The presence of analytes in the strip connecting the immunosorbing zone and the

absorbent means are then detected. It is nowhere taught by Ullman that any contents of the absorbent material are at any point to be recovered from the absorbent means.

Accordingly, since Ullman is directed to an analytic method in which all material introduced to the apparatus is retained therein in a “non-removably confined” absorbent means, Ullman fails to teach, or even to suggest, a method such that when the sample is contacted with the affinity binding composition the proteins are removed from the sample and the modified sample is thereby produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample, as is claimed.

As such, the Ullman reference does not support a conclusion that “all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods **with no change in their respective functions**” (emphasis added). Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007 / Notices at 57529, *citing KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1395 (US 2007).

Moreover, in the Final Office Action of October 10, 2007, the Examiner acknowledges that Ullman does not describe a plurality of receptor types having different protein binding specificities relative to each other, each receptor type immobilized on separate particles, the particles present as a mixture in the affinity binding composition (Final Office Action, page 7, lines 17-19). However, the Examiner seeks to provide support for combining Ullman and Rubenstein by asserting that Rubenstein “describes a plurality of receptor types having different protein binding specificities relative to each other (see *e.g.,* col. 6, line 5, "different enzyme labeled antibodies"; see also, line 20, "panel 'of allergens"; see *also,* lines 35-36, "different receptor")., each receptor type immobilized on separate particles (see *e.g.,* col. 6, line 7, "groups of microspheres"; see *also,* lines 15-16, "distinct groups of microspheres"; see *also,* line 34, "groups of microspheres"), the particles present as a mixture in said affinity binding composition (Final Office Action,

paragraph spanning pages 7-8).

However, as discussed above, the cited passages of Rubenstein do not teach what the Examiner alleges. Rubenstein's own explanation of the cited terms is not consistent with the Examiner's assertion. The relevant passage of Rubenstein at column 5, lines 44-65, is reproduced below for convenience:

> A preferred solid phase system of the present invention comprises plural groups of microspheres entrapped in discrete zones, preferably in a predetermined pattern, within the matrix. Each group of microspheres is bound, prior to entrapment, with a different receptor, such as an antibody or antigen capable of capturing a different ligand of interest. Accordingly, in one embodiment of the invention, each group of microspheres comprises a population of microspheres bound with the same antibody, antigen or other receptor selected for use in the assay. Alternatively, a group of microspheres may comprise a mixture of microspheres to which are bound different receptors. For example, in the case of an immunoassay for an antigen, each group of microspheres may comprise at least two subpopulations of microspheres wherein each subpopulation is bound with an antibody, preferably a monoclonal antibody, capable of binding with a different determinant or epitope of the antigen. Preferably, the monoclonal antibodies bound with the subpopulations of microspheres comprising a distinct group of microspheres are selected to have a specific reactivity with non-interfering epitopes of the target ligand, thereby enhancing the sensitivity and specificity of the assay.

In light of the above passage from Rubenstein, one of ordinary skill in the art understands that each group of microspheres in a discrete zone, whether bearing a single receptor or multiple receptors, binds to "the target ligand," e.g., "the antigen," i.e., a single molecule. As such, Rubenstein at best fails to teach that the first and second solid phase matrices are present as a mixture in the binding composition, as is claimed. Instead, Rubenstein teaches in the above passage and throughout the reference that microspheres with binding specificities for different proteins are present in different zones, and not as a mixture. Accordingly, since Ullman is silent regarding a plurality of matrices with different receptors, neither reference teaches the claimed elements. Since Rubenstein was cited for precisely these elements, Rubenstein fails to remedy the several deficiencies of Ullman

Further, since Rubenstein makes clear to one of ordinary skill in the art that the flowthrough from the device of Rubenstein enters a waste trap from which no

effluent material is recovered, Rubenstein fails to teach, or even to suggest, a method such that when the sample is contacted with the affinity binding composition, the proteins are removed from the sample and the modified sample is thereby produced, in which the modified sample is not bound by a solid phase matrix; followed by recovery of the modified sample.

As such, since neither reference teaches or suggests recovery of the modified sample not bound by a solid phase matrix; and further, since neither reference teaches or suggests adsorbent species present as a mixture with receptors that have at least one mutual exclusivity with respect to a first and second protein, a *prima facie* case of obviousness is not made. It is clear from the disclosures of Rubenstein and Ullman themselves that the claimed elements cannot be found in the cited references absent the present disclosure itself. Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. *ATD Corp. v. Lydall, Inc.*, 48 USPQ2d 1321 (Fed. Cir. 1998). Nor do the references support "a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately." Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007 / Notices at 57529, *citing KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1395 (US 2007).

Group II: Claims 64 and 65

The claims of this group depend directly and indirectly, respectively, from Claim 63 and further include the elements that the affinity binding composition includes a third receptor immobilized on a third solid phase matrix, capable of specific binding to a third protein but not the first protein or the second protein, in which the third solid phase matrix contacts the first and second solid phase matrices. In addition to the above provided arguments, Appellants further submit that the combined references fail to teach or suggest a third receptor immobilized on a third solid phase matrix, capable of specific binding to a third protein but not the first or second protein, in which the third solid phase matrix contacts the other solid phase

matrices. As discussed above, and without reiterating the entirety of the argument, since neither reference teaches or suggests recovery of the modified sample not bound by a solid phase matrix; and further, since neither reference teaches or suggests adsorbent species present as a mixture with receptors that have at least one mutual exclusivity with respect to a first and second protein, a *prima facie* case of obviousness is not made. As such, one of ordinary skill in the art would neither learn nor find suggestion of the additionally claimed matrix and specificity elements present in contact with the other matrices by reading the combined references.

Group III: Claims 66 and 67

The claims of this group depend directly and indirectly, respectively, from Claim 63 and further include the elements that the affinity binding composition includes a fourth receptor immobilized on a fourth solid phase matrix, capable of specific binding to a fourth protein but not the first protein, the second protein or the third protein, in which the fourth solid phase matrix contacts the first, second, and third solid phase matrices. In addition to the above provided arguments, Appellants further submit that the combined references fail to teach or suggest a fourth receptor immobilized on a fourth solid phase matrix, capable of specific binding to a fourth protein but not the first second or third protein, in which the fourth solid phase matrix contacts the other solid phase matrices. As discussed above, and without reiterating the entirety of the argument, since neither reference teaches or suggests recovery of the modified sample not bound by a solid phase matrix; and further, since neither reference teaches or suggests adsorbent species present as a mixture with receptors that have at least one mutual exclusivity with respect to a first and second protein, a *prima facie* case of obviousness is not made. As such, one of ordinary skill in the art would neither learn nor find suggestion of the additionally claimed matrix and specificity elements present in contact with the other matrices by reading the combined references.

Group IV: Claims 68 and 69

The claims of this group depend directly and indirectly, respectively, from Claim 66 and further include the elements that the affinity binding composition

further includes a fifth receptor immobilized on a fifth solid phase matrix, capable of specific binding to a protein but not the first protein, the second protein, the third protein or the fourth protein, in which the fourth solid phase matrix contacts the first, second, third and fourth solid phase matrices. In addition to the above provided arguments, Appellants further submit that the combined references fail to teach or suggest a fifth receptor immobilized on a fifth solid phase matrix, capable of specific binding to a fifth protein but not the other proteins, in which the fifth solid phase matrix contacts the other solid phase matrices. As discussed above, and without reiterating the entirety of the argument, since neither reference teaches or suggests recovery of the modified sample not bound by a solid phase matrix; and further, since neither reference teaches or suggests adsorbent species present as a mixture with receptors that have at least one mutual exclusivity with respect to a first and second protein, a *prima facie* case of obviousness is not made. As such, one of ordinary skill in the art would neither learn nor find suggestion of the additionally claimed matrix and specificity elements present in contact with the other matrices by reading the combined references.

Group V: Claims 52, 84, 85, 88, 111 and 113

As described above, independent claim 84 is drawn to a method for producing and recovering a modified sample, the method including removing at least a first protein and a second protein from a sample, the removing step including contacting the sample with an affinity binding composition including a plurality of solid phase matrices with a plurality of receptors having different protein binding specificities immobilized thereon such that each solid phase matrix has a different protein binding specificity, in which each the solid phase matrix is a plurality of particles and the plurality of solid phase matrices are present as a mixture in the binding composition, so that when the sample is contacted with the affinity binding composition, the at least two proteins become bound to the affinity binding composition and the proteins are thereby removed from the sample such that the modified sample is produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample.

The Appellants submit that the combined teachings of Ullman in view of Rubenstein fail to teach or suggest each and every element of the claimed invention. Appellants submit that the arguments made above for Group I apply to the claims of the present group. Briefly, and without reiterating the entirety of the argument, since neither reference teaches or suggests recovery of the modified sample not bound by a solid phase matrix; and further, since neither reference teaches or suggests adsorbent species present as a mixture with receptors that have at least one mutual exclusivity with respect to a first and second protein, a *prima facie* case of obviousness is not made. As such, one of ordinary skill in the art would neither learn nor find suggestion of the plurality of matrices and specificity elements present in contact with the other matrices claimed by this claim group by reading the combined references.

Group VI: Claim 89

Claim 32 depends from any of Claims 63, 84 or 85 and further includes the element in which the receptors are recombinantly produced. In addition to the above provided arguments, Appellants further submit that although the references discuss the use of monoclonal antibodies, neither reference teaches, explicitly or implicitly, the use of recombinantly produced receptors. Accordingly, the cited references additionally fail to teach the limitations of this claim group.

Group VII: Claim 32

Claim 32 depends from any of Claims 63, 84, 85, 88, or 106 and further includes the element in which at least 50% by weight of all proteins in the sample are removed. In addition to the above provided arguments, Appellants further submit that the cited references fail to teach the removal of any percentage or proportion of total protein from the sample. Accordingly, the references additionally fail to teach the limitations of this claim group.

Group VIII: Claim 52

Claim 52 depends from any of Claims 63, 84 or 85 and further includes the step of analyzing a plurality of proteins remaining in the modified sample. In addition

to the above provided arguments, Appellants further submit that the cited references nowhere teach the analysis of proteins remaining in the modified sample. Accordingly, the references additionally fail to teach the limitations of this claim group.

Group IX: Claim 62

Claim 62 depends from any of Claims 63, 84 or 85 and further includes the element in which at least one of the proteins is present at higher abundance than at least one of the plurality of proteins remaining in the sample after removal of the proteins. In addition to the above provided arguments, Appellants further submit that the cited references nowhere discuss the greater abundance of a protein to be removed relative to any other protein in the sample. Accordingly, the references additionally fail to teach the limitations of this claim group.

In view of the arguments above, the Appellants submit that the combined teachings of Ullman et al. and Rubenstein fail to make obvious the claims of Groups I-IX and respectfully request reversal of this rejection.

SUMMARY

I. Claims 32, 52, 62-69, 84, 85, 88, 89, 104-107 and 110-113 are not anticipated under 35 U.S.C. § 102(b) by Hutchens *et al.* (US 6,225,047) because Hutchens *et al.* fails to teach a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, in which each solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture, as is claimed.

II. Claims 62-64, 66, 84-85, 88-89, 104 and 110-113 are not anticipated under 35 U.S.C. § 102(b) by Rubenstein (US 5,879,881) because Rubenstein fails to teach a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a

second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, in which each solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture; and a method such that when the sample is contacted with the affinity binding composition the proteins are removed from the sample and the modified sample is thereby produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample, as is claimed.

III. Claims 62-64, 66, 84-85, 88-89, 104-107 and 110-113 are not obvious under 35 U.S.C. § 103(a) over Ullman *et al.* (US 5,137,808) in view of Rubenstein (US 5,879,881) because Rubenstein fails to remedy the fundamental deficiencies in the teachings of Ullman *et al.*: namely, an affinity binding composition including a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, in which the first and second solid phase matrices are present as a mixture in the binding composition; in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample.

RELIEF REQUESTED

The Appellants respectfully request that the rejection of Claims 32, 52, 62-69, 84, 85, 88, 89, 104-107 and 110-113 under 35 U.S.C. § 102 and the rejection of Claims 62-64, 66, 84-85, 88-89, 104-107 and 110-113 under 35 U.S.C. § 103 be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: February 7, 2008

By: /Bret Field, Reg. No. 37,620/
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CLAIMS APPENDIX

32. The method of claim 63, 84, 85, 88, or 106 in which at least 50% by weight of all proteins in the sample are removed.

52. The method of claim 63, 84, or 85, further including the step of analyzing a plurality of proteins remaining in the modified sample.

62. The method of claim 63, 84, or 85, in which at least one of the proteins is present at higher abundance than at least one of the plurality of proteins remaining in the sample after removal of the proteins.

63. A method for producing and recovering a modified sample, said method including:

removing at least a first protein and a second protein from a sample, said removing step including contacting said sample with an affinity binding composition including a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to said first protein but not said second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to said second protein but not said first protein, in which each said solid phase matrix is a plurality of particles and said first and second solid phase matrices are present as a mixture in said binding composition;

so that when said sample is contacted with said affinity binding composition, said first protein present in said sample binds to said first receptor present on said first solid phase matrix such that said first protein is removed from said sample and said second protein present in said sample binds to said second receptor present on said second solid phase matrix such that said second protein is removed from said sample and said modified sample is thereby produced, in which said modified sample is not bound by a solid phase matrix; and

recovering said modified sample.

64. The method of claim 63, in which the affinity binding composition further

includes:

a third receptor immobilized on a third solid phase matrix, capable of specific binding to a third protein but not the first protein or the second protein.

65. The method of claim 64, in which the third solid phase matrix contacts the first and second solid phase matrices.

66. The method of claim 63, in which the affinity binding composition further includes:

a fourth receptor immobilized on a fourth solid phase matrix, capable of specific binding to a fourth protein but not the first protein, the second protein or the third protein.

67. The method of claim 66, in which the fourth solid phase matrix contacts the first, second, and third solid phase matrices.

68. The method of claim 67, in which the affinity binding composition further includes:

a fifth receptor immobilized on a fifth solid phase matrix, capable of specific binding to a protein but not the first protein, the second protein, the third protein or the fourth protein.

69. The method of claim 68, in which the fifth solid phase matrix contacts the first, second, third, and fourth solid phase matrices.

84. A method for producing and recovering a modified sample, said method including:

removing at least a first protein and a second protein from a sample, said removing step including contacting said sample with an affinity binding composition including a plurality of solid phase matrices with a plurality of receptors having different protein binding specificities immobilized thereon such that each solid phase matrix has a different protein binding specificity, in which each said solid phase

matrix is a plurality of particles and said plurality of solid phase matrices are present as a mixture in said binding composition,

so that when said sample is contacted with said affinity binding composition, said at least two proteins become bound to said affinity binding composition and said proteins are thereby removed from the sample such that the modified sample is produced, in which said modified sample is not bound by a solid phase matrix; and

recovering said modified sample.

85. The method of claim 63, or 84, in which the sample is passed through a column containing the affinity binding composition to produce the modified sample, in which the affinity column has a fluid inlet and a fluid outlet, and in which the modified sample is collected at the fluid outlet.

88. The method of claim 63, 84, or 85, in which the receptors are antibodies or antibody fragments that specifically bind to the proteins.

89. The method of claim 63, 84, or 85, in which the receptors are recombinantly produced.

104. The method of claim 63, 84, or 85, in which at least one of the proteins is selected from the group consisting of: immunoglobulins, albumin, transferrin, haptoglobin, α_1-antitrypsin, hemopexin, α_1-acid glycoprotein, α2 HS glycoprotein, myosin, transthyretin, α_1-antichymotrypsin, apolipoprotein Al, α_2-macroglobulin, fibrinogen, and prealbumin, and combinations thereof.

105. The method of claim 63, 84, or 85, in which at least two of the proteins are selected from the group consisting of: immunoglobulins, albumin, transferrin, haptoglobin, α_1-antitrypsin, hemopexin, α_1-acid glycoprotein, α2 HS glycoprotein, myosin, transthyretin, α_1-antichymotrypsin, apolipoprotein Al, α_2-macroglobulin, fibrinogen, and prealbumin.

106. The method of claim 63, 84, 85, or 88, in which at least three of the proteins

are selected from the group consisting of: immunoglobulins, albumin, transferrin, haptoglobin, α_1-antitrypsin, hemopexin, α_1-acid glycoprotein, α2 HS glycoprotein, myosin, transthyretin, α_1-antichymotrypsin, apolipoprotein AI, α_2-macroglobulin, fibrinogen, and prealbumin.

107. The method of claim 63, 84, or 85, in which at least four of the proteins are selected from the group consisting of: immunoglobulins, albumin, transferrin, haptoglobin, α_1-antitrypsin, hemopexin, α_1-acid glycoprotein, α2 HS glycoprotein, myosin, transthyretin, α_1-antichymotrypsin, apolipoprotein AI, α_2-macroglobulin, fibrinogen, and prealbumin.

110. The method of claim 63, in which at least three proteins are removed from a sample.

111. The method of claim 84, in which at least three proteins are removed from a sample.

112. The method of claim 63, in which at least four proteins are removed from a sample.

113. The method of claim 84, in which at least four proteins are removed from a sample.

EVIDENCE APPENDIX

No evidence that qualifies under this heading has been submitted during the prosecution of this application, and as such it is left blank.

RELATED PROCEEDINGS APPENDIX

As stated in the *Related Appeals and Interferences* section above, there are no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal. As such this section is left blank.